A Generalized Psychological Hyperreactivity to Acute Stressors in Hypertensives

Nyklicek, I.; Bosch, A.; Nieuw Amerongen, A.V.

Published in:
Biological Psychology

Publication date:
2005

Document Version
Publisher's PDF, also known as Version of record

Available online at www.sciencedirect.com
SCIENCE DIRECT
Biological Psychology 70 (2005) 44–51
BIOLOGICAL PSYCHOLOGY
www.elsevier.com/locate/biopsycho

A generalized physiological hyperreactivity to acute stressors in hypertensives

Ivan Nyklíček [a,*], Jos A. Bosch [b,c], Arie V. Nieuw Amerongen [b]

[a] *Department of Psychology and Health, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands*
[b] *Department of Dental Basic Sciences, Section Oral Biochemistry, Academic Center for Dentistry Amsterdam (ACTA), Vrije University, Amsterdam, The Netherlands*
[c] *School of Sports and Exercise Sciences, The University of Birmingham, Birmingham, UK*

Received 17 May 2004; accepted 11 November 2004
Available online 16 February 2005

Abstract

Hypertensives have consistently been found to have a more reactive cardiovascular system than normotensives. In the present study, it was examined whether this enhanced cardiovascular stress reactivity generalizes to the hypothalamus–pituitary–adrenal (HPA) axis and the immune system. Forty-two unmedicated hypertensives and 21 normotensive controls performed five passive coping and active coping stressful tasks in the laboratory. In addition to the expected greater mean diastolic blood pressure reactivity to the tasks, hypertensives exhibited enhanced (baseline corrected) task salivary cortisol and secretory immunoglobulin A (S-IgA) levels. Moreover, correlations were found between blood pressure responses and task related cortisol activity and between baseline blood pressure levels and task-induced S-IgA levels. These results indicate that hypertensives not only have a hyperreactive cardiovascular system, but also an enhanced HPA axis and immune system reactivity to stress. A central stress mechanism may be responsible for the heightened generalized stress response in hypertensives.

Keywords: Hypertension; Cortisol; Immunoglobulin A; HPA; Reactivity

1. Introduction

When confronted with laboratory stressors, hypertensives have been found to have a more reactive cardiovascular system than normotensives (see Fredrikson and Matthews, 1990; Manuck et al., 1990, for reviews). This has been established for various stressors, including passive physical stressors, such as the cold pressor task, and active psychological stressors, such as mental arithmetic (Manuck et al., 1990; Tuomisto, 1997). A hyperactive cardiovascular system has also been reported in young borderline hypertensives, and even in offspring of hypertensives (Fredrikson and Matthews, 1990). Indeed, cardiovascular hyperreactivity is predictive of, and perhaps even contributes to, the development of hypertension (e.g., Brod, 1963; Esler et al., 1977; Julius, 1991; Light et al., 1992). This cardiovascular hyperreactivity has been proposed to be a consequence of a hyperreactive sympathetic branch of the autonomic nervous system (Brod, 1963; Esler et al., 1977), which has been demonstrated especially in the early stages of the hypertensive process (Eich et al., 1966; Eliasson et al., 1983; Esler et al., 1977; Guzzetti et al., 1988; Julius, 1991).

Sympathetic hyperactivity often goes together with enhanced activation of the hypothalamic–pituitary–adrenal (HPA) axis (Cacioppo et al., 1998; Lovallo et al., 1990; Neville and O'Hare, 1984), and enhanced stress-reactivity of the HPA axis has been associated with an increased risk for hypertension (al'Absi et al., 1994; Fredrikson et al., 1991). For instance, hypertensives are found to exhibit larger cortisol elevations during mental stress (al'Absi et al., 1994; Baumann et al., 1973). Likewise, normotensives with a parental history of hypertension show stronger cortisol (al'Absi et al., 1998; Fredrikson et al., 1991) and ACTH responses to stress (al'Absi et al., 1998). Although these finding have not been supported by all studies (Bohlin et al.,

* Corresponding author. Tel.: +31 13 4662391; fax: +31 13 4662370.
E-mail address: i.nyklicek@uvt.nl (I. Nyklíček).

0301-0511/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2004.11.013

1986; Hollenberg et al., 1981), the balance of evidence indicates that hypertension may be associated with altered HPA function during stress.

Another physiological system that is affected by sympathetic activity is the immune system (Benschop et al., 1996; Elenkov et al., 2000). Numerous studies have demonstrated that the immune system responses to acute stress (e.g., the mobilization of lymphocytes into the circulation, the secretion of immunoglobulins) is causally dependent on concomitant sympathetic nervous system responses (Benschop et al., 1996; Mills et al., 2003). Immunological abnormalities have been suggested to play a role in essential hypertension (al'Absi and Arnett, 2000; Chen and Schachter, 1993; Dzielak, 1992; Norman et al., 1985), as well as in the development of atherosclerosis. Hence, the link between autonomic hyperreactivity and the development of cardiovascular disease may be mediated through immunological pathways (Bosch et al., 2003a,b). Because hypertensives are characterized by elevated sympathetic activation, and possibly HPA reactivity, their immune system may be hyperreactive as well. Indeed, recently Mills et al. (2003) demonstrated enhanced immunological response (CD62L and CD11a expression) to a psychological stressor in hypertensives. However, since blood velocity is an important determinant of this mobilization response (Benschop et al., 1996; Uchino et al., 1995) and the extent of this immunological response correlates with increases in systolic blood pressure (SBP) (Uchino et al., 1995), the effects obtained by Mills et al. may be due to blood circulatory effects.

In the present study, we took a multi-systems approach that examined whether hypertensives exhibit exaggerated cardiovascular reactivity simultaneously with an enhanced activity of the HPA axis and the immune system. Additionally, we examined the extent to which responses of these three systems were intercorrelated. For this purpose multiple laboratory stressors were employed, ranging from passive coping physical (electric current) and psychological (gruesome video clips) stressors to active coping psychological stressors such as the mental arithmetic and the speech stressor task. Secretory immunoglobulin A (S-IgA) was used as the immunological outcome variable (i) in order to exclude the possibility of potential associations being the result of blood circulatory effect and (ii) because this main immunoglobulin in mucosal secretions (forming a first line of immunological defense) has been shown to respond very sensitively to sympathetic nervous system activation (Bosch et al., 2001; Bosch et al., 2002; Proctor and Carpenter, 2002).

2. Methods

2.1. Participants

Sixty-three participants were selected from a large pool of individuals that took part in a population blood pressure screening study (Nyklíček et al., 1999a), to yield groups of 42 untreated hypertensives and 21 normotensive controls. The groups were matched on age and gender (with both genders represented approximately equally), body mass index (BMI), alcohol use, smoking, physical exercise, and years of education. The definition of hypertension was based on the mean of at least three valid resting blood pressures at the participants' homes during the population screening study (Nyklíček et al., 1999a). A mean systolic blood pressure of at least 140 mmHg or a mean diastolic blood pressure (DBP) of equal to or higher than 90 mmHg was considered hypertensive.

As recommended by Shapiro et al. (1996), participants were asked to refrain from using alcohol on the day of the experiment, from caffeine consumption for at least 3 h, and from smoking for at least 2 h prior to the laboratory session. The subjects received NLG 40 (approximately US$ 20) for their participation.

2.2. Cardiovascular measures

In order to check whether blood pressure status had changed between the screening and the laboratory session, blood pressure was measured twice immediately before and twice after the session, using the same device as in the population screening home measurements: a Philips HP 5330 automatic oscillometric sphygmomanometer.

During the entire experiment blood pressure was measured using an Ohmeda 2300 Finapres. The signal was recorded continuously by a cuff placed around the middle finger of the left hand of the participants (all subjects were right-handed). An electrocardiogram (ECG) was obtained from disposable Hellige Ag–AgCl electrodes that were placed on the sternum and the lateral margin of the chest. The ECG was recorded using a Beckman R611 with a time constant of 0.3 s and a 30 Hz high frequency cut-off filter.

2.3. Saliva collection

Saliva was collected using Salivettes (Sarstedt), which were held in the mouth for 2 min, without stimulation by chewing. Samples were stored at $-20\ ^{\circ}C$ until analysis.

Cortisol was determined using a biotin-streptavidin immunoassay with TR-fluorometric end point determination, as described in detail by Dressendörfer et al. (1992).

S-IgA was determined by a sandwich ELISA, as described in detail by Bosch et al. (2001). Total salivary protein was determined using the bicinchoninic acid method (Pierce, Rockford, IL; as described by Bosch et al., 1996). All samples of the same subject were analyzed in the same assay run. The intra-assay reliability (CV%) was $<5\%$.

2.4. Procedure

Upon arrival at the laboratory, participants were seated in a comfortable chair. After an informed consent was obtained

from the participants, physiological equipment was attached and a mood checklist was completed. Blood pressure was measured twice with a 2-min interval between the measurements using the oscillometric sphygmomanometer described above. During the 2-min interval, the first saliva sample was collected. The computer started the experimental program. All tasks were followed by a brief rest period of 5 min, except for the last rest period, which lasted 10 min. After all rest periods, except after the mental arithmetic task (see below), saliva samples were collected. The whole experiment lasted 120 min. After being detached from the measurement equipment, blood pressure was again measured twice using the oscillometric sphygmomanometer and a final sample of saliva was obtained (on average 15 min after the final rest period).

When departing, the participants were given another Salivette tube in order to collect a sample by themselves the following morning. It was stressed that the sample should be taken immediately after awakening. In addition, it was requested to fill out a short form in which it was asked at what time the participants woke up and what the interval was between the time of awakening and the time of saliva collection. These samples were returned by post the same day and stored at −20 °C until analysis, together with the samples obtained on the previous day.

The participants performed the experimental tasks in the same order as described below. This order was applied since (i) our main aim was to examine simultaneous responses in the cardiovascular, HPA-axis, and immunological systems across tasks, rather than examining specific responses of each system to specific tasks and (ii) our secondary aim was to test differences in pain sensitivity between the hypertensive and normotensive groups, data on which have been reported elsewhere (Nyklíček et al., 1999b). For the latter purpose, the pain task had to be administered first in order to circumvent potential effects of stress-induced analgesia (Amit and Galina, 1988) by preceding mental stressors. In addition, potential effects of anxiety related to anticipation of receiving painful electric current stimulation on responses to the other tasks were expected to be minimal when the pain task was administered before the mental stress tasks.

2.4.1. Music perception

A relaxing music fragment (new age) of 290 s duration was presented with the instruction just to ‘‘listen attentively to the music’’. In addition, after the music, some questions were asked ‘‘about the feelings you think are expressed by the music’’. This task was intended to be a fake-task, providing an opportunity for the subjects to get familiar with performing a task in the present setting, resulting in a more relaxed state before starting the pain conditions.

2.4.2. Pain stimulation

Constant electric current was delivered to the ventral side of the left forearm of the participants using a concentric electrode. The current was a 60 Hz bipolar 50%-duty square pulse, of which the intensity was raised in a continuous linear way and could reach a maximum of 6 mA. The selection of the maximum intensity level was based on previous research (Tursky, 1974) as well as a small pilot study. During the task, the participants were asked to indicate when the stimulus reached the point to be ‘‘unpleasant to a degree that the subject wanted to terminate the current’’ (pain tolerance), at which point the stimulation stopped (Nyklíček et al., 1999b).

2.4.3. Mental arithmetic

A mental arithmetic task based on the protocol used by Van Zijderveld et al. (1993) was applied in the present study. During 5 s, three consecutive one or two digit numbers appeared on the computer screen, which had to be added by the participant in 7 s. Participants were instructed to try to reach the most difficult level as quickly as possible. Although this level was quite difficult to reach, the participants were told that it ‘‘appeared to be reasonably well manageable by an average Dutch citizen’’, in order to enlarge the motivation of the participants.

2.4.4. Speech

The second active coping task was a free speech task largely based on a protocol designed by Krantz et al. (1991). After a 90 s preparation, the participants had to speak in front of a camera for 3 min about their personal faults and undesirable habits. They were instructed not to talk about trivial things, but to be honest and open. Furthermore, they were encouraged to give an attractive presentation with a logical structure.

2.4.5. Films

The passive coping tasks consisted of watching two film fragments depicting stressful everyday life scenes (Hettema et al., 1989). The first movie, called Accident (225 s), shows a woman who gets her fingers badly cut when trying to mend a kitchen mixer. The second movie (Interruption; 690 s) is about a mechanic, who gets interrupted all the time while trying to repair a car, which he was told was an emergency task.

2.5. Data reduction and statistical analysis

Regarding cardiovascular parameters, for each task and rest period, means and standard deviations were determined of: (i) inter-beat-interval (IBI), defined as the time in ms between successive R-waves, (ii) systolic blood pressure, and (iii) diastolic blood pressure. The mean values of the last 4 min of the resting periods preceding the tasks were used as baseline. The last 4 min of the last (10 min) rest period were used for determination of cardiovascular recovery values. After computing the mean values, cardiovascular responses were defined as the true difference scores (T) between the mean task value and the

mean baseline value corrected for its reliability, according to Fahrenberg et al. (1995):

$$T_{ij} = y_{ij} - [x_{.j} + r_{xxj}(x_{ij} - x_{.j})]$$

where y_{ij} and x_{ij} are the respective task and baseline score for subject i and condition j, $x_{.j}$ is the mean and r_{xxj} is the reliability coefficient of baseline measures across subjects.

The distributions of task-related salivary cortisol and S-IgA concentration levels were skewed. Therefore, these variables were log transformed before being used in the analyses. For stressor related activity, the relevant task values were used controlling for the first (baseline) values, which were entered as covariates. The last sample, obtained approximately 15 min after the last rest period, was regarded as a measure of recovery.

Based on the findings in the laboratory, blood pressure status appeared to be changed in five participants. These five persons were excluded from all analyses (including these subjects would not change the results appreciably). As a result of excessive noise on the Finapres signal (three persons), having removed the Finapres cuff for being too tight (one person), not having talked during the speech (one person), and missing values for one or more cortisol samples (five participants), data from these individuals were excluded from the relevant analyses. When a low quantity of saliva was produced by a participant, priority was given to cortisol determination. As a result of this procedure, S-IgA and total protein values were missing for another five participants. Three additional persons were identified as outliers regarding S-IgA (>2 S.D. from the mean) and were removed from the data.

The following statistical analyses were performed using the SPSS statistical software package (Version 11.5). First, differences between groups on background variables were tested by means of *t*-tests for independent groups. To test differences between groups on most dependent variables Group × Sex × Condition multivariate repeated measures analysis of variance (MANOVA) were applied. Unique sums of squares were used, which controls for every other effect when testing the significance of an effect.

Time of measurement was used as a covariate for the salivary measures in order to control for effects of circadian variation (all sessions started between 1:00 p.m. and 7:00 p.m.). Because salivary flow rate (ml/min) was not recorded, total protein was used as a covariate for the analyses on S-IgA. The rationale behind this approach is that dilution effects due to variation in flow rate will similarly affect total protein concentration and S-IgA concentration. Hence, variance in S-IgA concentration that is secondary to variation in flow rate will be removed by controlling for total protein concentration. Interrelationships between cardiovascular, cortisol, and S-IgA activity were examined by partial Pearson's product-moment correlations between the sets of variables, controlling for age and/or sex, if one or both of these variables showed a (marginally) significant correlation with one of the outcome measures.

3. Results

No significant differences between the groups were found on any of the matching variables (see Table 1). Data regarding pain sensitivity showed that among women, hypertensives demonstrated higher pain threshold and pain tolerance levels compared to normotensives, while no differences were obtained among men. More details concerning pain sensitivity are outside the scope of the present article and have been published elsewhere (Nyklíček et al., 1999b).

3.1. Cardiovascular measures

First, baseline differences between the groups were examined by means of 2 (Group) × 2 (Gender) analyses of variance. For none of the variables a Group × Gender interaction or a Gender main effect was obtained (all $p > .10$). With respect to IBI, a significant Group main effect emerged [$F(1,48) = 4.86$, $p < .05$], showing higher resting heart rates in hypertensives, compared with normotensives (Table 2). As one may expect, large differences were found between the groups on baseline SBP [$F(1,48) = 42.66$, $p < .001$] and DBP [$F(1,48) = 72.55$, $p < .001$] (Table 2).

Regarding cardiovascular responses, no three-way interaction (Group × Gender × Condition) was obtained for any variable. For IBI, only the main effect of Condition [$F(3,46) = 68.57$, $p < .001$] and the Gender × Condition interaction [$F(3,46) = 4.36$, $p = .009$] were significant, indicating heart rate acceleration only during mental arithmetic and especially the speech task (Table 2), while the latter evoked strong accelerations particularly in women. Also for blood pressure, significant main effects of Condition were obtained [$F(3,46) = 53.62$, $p < .001$ for SBP and $F(3,46) = 67.58$, $p < .001$ for DBP]; the responses were strongest during the speech task and lowest during the films. For SBP no other significant effects emerged, while DBP responses were stronger in hypertensives than in normotensives [$F(1,48) = 4.45$, $p = .040$] (Table 3).

Table 1
Characteristics of the sample: means and standard deviations or percentages

Variable	Normotensives ($N = 20$)	Hypertensives ($N = 37$)
Baseline home SBP	113.5 (8.3)	142.4 (12.5)***
Baseline home DBP	72.6 (5.5)	95.3 (4.6)***
Male (%)	55.0	52.7
Age	44.8 (5.6)	43.8 (6.0)
Body mass index	24.4 (2.3)	25.8 (3.8)
Married or living together (%)	95.0	91.7
Years of education	11.2 (3.5)	10.9 (3.1)
Employment (%)	80.0	76.4
Smoker (%)	55.0	46.1
Coffee (cups per day)	5.55 (2.63)	5.43 (2.81)
Alcohol (glasses per week)	8.1 (9.0)	10.9 (10.5)
Sport (hours per week)	1.10 (1.51)	1.13 (1.48)

*** $p < .001$.

Table 2
Cardiovascular, cortisol, and S-IgA parameters related to the different periods within the experiment: means and standard deviations

Variable	IBI	SBP	DBP	Cortisol	S-IgA
Baseline					
NT	831 (109)	120 (13.6)	78.8 (7.12)	0.50 (0.30)	2.03 (0.40)
HT	766 (99)	151 (23.2)	101.0 (16.71)	0.57 (0.30)	2.13 (0.43)
Pain task					
NT	836 (103)	147 (17.3)	88.9 (8.98)	0.38 (0.34)	2.15 (0.40)
HT	774 (109)	180 (20.8)	113.2 (18.47)	0.44 (0.29)	2.40 (0.40)
Mental arithmetic					
NT	798 (92)	155 (23.8)	94.3 (9.63)		
HT	745 (108)	186 (26.8)	118.9 (19.89)		
Speech					
NT	769 (96)	160 (25.5)	97.3 (9.74)	0.33 (0.27)	2.00 (0.42)
HT	719 (112)	194 (27.0)	124.2 (22.31)	0.44 (0.27)	2.35 (0.42)
Films					
NT	896 (114)	139 (13.9)	88.6 (9.34)	0.24 (0.31)	1.85 (0.50)
HT	820 (111)	170 (23.6)	113.6 (21.02)	0.37 (0.27)	2.32 (0.35)
Recovery					
NT	857 (121)	132 (13.4)	87.5 (8.54)	0.32 (0.29)	2.15 (0.30)
HT	801 (110)	162 (25.1)	111.6 (20.23)	0.40 (0.30)	2.26 (0.43)

Note: NT, normotensives; HT, hypertensives. Saliva samples were not obtained after mental arithmetic; cortisol is in log(nmol/l) and S-IgA is in log(μg/ml).

No other effects were significant for cardiovascular variables.

3.2. Salivary cortisol

Apart from a significant effect of the covariate time ($\beta = -.65$, $p < .001$), reflecting the expected diurnal effect, no effects were found with regard to baseline cortisol levels.

For the task related and baseline corrected levels, a significant main effect of Condition emerged [$F(2,44) = 5.67$, $p = .006$], showing lowest levels after the film clips (Fig. 1). In addition, a significant Group main effect [$F(1,45) = 6.05$, $p = .018$] showed that hypertensive participants had higher task related levels than normotensives (Table 3; Fig. 1). No other significant effects emerged.

Table 3
Mean cardiovascular responses and baseline-corrected cortisol and S-IgA levels across all tasks: means and standard deviations

Variable	Normotensives	Hypertensives
IBI response	−14.50 (36.65)	−11.63 (29.86)
SBP response	25.36 (12.28)	29.11 (10.42)
DBP response	10.52 (3.45)	13.35 (5.77)*
Log cortisol task levels	0.33 (0.30)	0.41 (0.28)*
Log S-IgA task levels	2.02 (0.44)	2.36 (0.38)**

* $p < .05$.
** $p < .01$.

Regarding morning cortisol, both the time of sampling and the interval between the time of awakening and the time of sampling did not correlate with morning cortisol levels ($r < .10$, $p > .10$). The hypertensive and normotensive groups had similar morning cortisol levels: $M = 15.51$ nmol/l (S.D. = 6.85) and $M = 14.48$ nmol/l (S.D. = 6.55), respectively, $t(50) = 0.58$, $p > .10$.

3.3. Secretory immunoglobulin A

No effects were found for baseline levels of S-IgA (all $F < 1.0$, $p > .10$). For the task-related (baseline corrected) levels, however, several significant effects were obtained. A main effect of Condition [$F(2,36) = 6.92$, $p = .003$] indicated highest levels after the pain task and lowest levels after the films (Table 2). This effect was somewhat more evident in normotensive individuals, as reflected by a nearly significant trend for a Group × Condition interaction effect [$F(2,36) = 3.13$, $p = .056$] (Fig. 2). Finally, a Group main effect indicated that hypertensives had overall higher task related (baseline corrected) levels than their normotensive counterparts [$F(1,37) = 10.38$, $p = .003$] (see Fig. 2).

3.4. Relationships between cardiovascular, cortisol, and immunoglobulin A activity

The partial correlations between cardiovascular variables on the one hand, and cortisol, and S-IgA parameters, on the other hand, are presented in Table 4. Data reflect

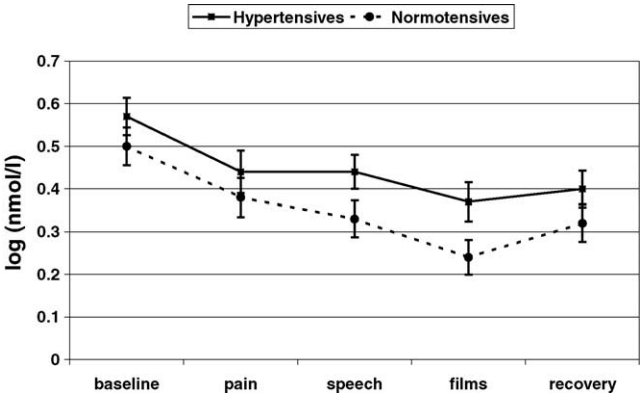

Fig. 1. Salivary cortisol levels (log (nmol/l)) in hypertensives and normotensives.

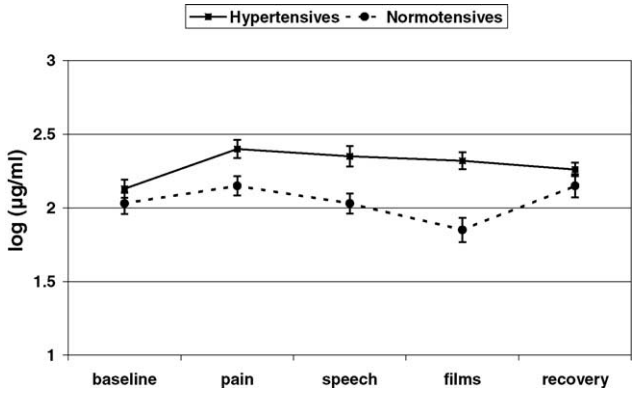

Fig. 2. Secretory IgA levels (log (μg/ml)) in hypertensives and normotensives.

Table 4
Correlations between blood pressure variables and cortisol and S-IgA parameters, controlled for sex and time

	Cortisol		S-IgA	
	Baseline	Tasks	Baseline	Tasks
IBI: baseline				
SBP: baseline		0.29*		0.32*
DBP: baseline		0.30*		0.32*
IBI: response		−0.26#		
SBP: response		0.32*		
DBP: response		0.29*		

Note: The task-related responses indicate means across all tasks. Only correlations $r > 0.25$ ($p < 0.10$) are depicted.
* $p < 0.05$.
# $p < 0.10$.

correlations between overall mean responses across the tasks.

Both baseline blood pressure and mean blood pressure responses (both SBP and DBP) correlated significantly positively with mean cortisol responses ($r > 0.29$, $p < 0.05$), but not with baseline cortisol. In analogue, no significant associations were obtained between either of the blood pressure measures and baseline S-IgA. However, both baseline SBP and DBP correlated positively with mean S-IgA task related levels (both $r = 0.32$, $p < 0.05$). IBI did not show correlations with either cortisol or S-IgA, except for a trend for an association between mean IBI shortening as a response to the tasks and mean task cortisol levels ($r = -.27$, $p = .075$).

Baseline cortisol did not correlate with either baseline or task related S-IgA. In contrast, a trend appeared for mean task related cortisol levels to be positively associated with baseline S-IgA ($r = .31$, $p = .055$), but not with mean task related S-IgA levels ($r = .17$, $p > .10$). Only for the pain task, the cortisol and S-IgA concentration levels were associated significantly ($r = .39$, $p < .02$).

4. Discussion

The present study investigated the relationships between cardiovascular, endocrine and immunological stress responses in hypertensives and normotensives. The results demonstrated that high blood pressure is associated with hyperresponsiveness in all three physiological systems. To the best of our knowledge this is the first study to take such a broad, multi-system approach to investigate physiological reactivity in hypertensives. Significant correlations between baseline blood pressure and both cortisol and S-IgA increases further confirm that hypertensive status is a predictor of immune and HPA-axis responses. Thus, our results demonstrate a generalized pattern of physiological hyperreactivity in hypertensives, which includes the cardiovascular system, the HPA-axis, and the immune system.

Regarding HPA axis activation, two earlier studies did not find a relationship between hypertension and plasma cortisol levels (Bohlin et al., 1986; Hollenberg et al., 1981). However, these earlier studies had a small number of participants (hypertensive patients $N = 24$ and $N = 15$, respectively), and used plasma total cortisol, which is not a good measure of the active unbound fraction of cortisol (Kirschbaum and Hellhammer, 1989). In contrast, to date most studies have reported elevated cortisol responses in hypertensives (al'Absi et al., 1994; Baumann et al., 1973) as well as in normotensive offspring of hypertensives (al'Absi et al., 1998; Fredrikson et al., 1991). Our findings are consistent with these reports.

Several researchers have suggested that alterations of the HPA axis activation may be an etiologic factor in essential hypertension (Litchfield et al., 1998; Watt et al., 1992). For instance, higher plasma cortisol levels have been found in the normotensive offspring of hypertensive parents, which is indicative for a genetic basis. A genetic basis may also exist regarding an altered sensitivity to cortisol in hypertensives. This idea was corroborated by the presence of a glucocorticoid receptor gene polymorphism in this group (Watt et al., 1992). Moreover, Walker et al. (1996) found higher dermal vasconstriction in hypertensives after topical application of cortisol and beclomethasone, indicating a higher sensitivity. This may constitute a risk factor for hypertension. It is currently unclear whether the results of the present study are a consequence of a primary HPA axis defect, or another mechanism, leading to the enhanced concerted stress response in hypertensives.

The immunological hyperresponsiveness in hypertensives that we observed in our study does not seem to be mediated by the concomitant HPA axis activity. Cortisol predominantly acts on a genomic level, and rapid (within minutes) immunomodulatory effects are therefore not biologically plausible (Bosch et al., 2002; Sapolsky et al., 2000). Indeed, animal studies demonstrate that the effect of glucocorticoids on S-IgA levels take effect only after approximately 24 h of administration. Conversely, there is ample evidence for a modulatory effect of the autonomic nerves on S-IgA secretion (Bosch et al., 2002; Proctor and Carpenter, 2002). Sympathetic nervous system hyperreactivity has been observed in a substantial part of hypertensives (e.g., Esler et al., 1977; Julius, 1991), and the rapid effects of S-IgA levels found in the present study likely reflect autonomic nervous system activation (Bosch et al., 2002).

Regarding the altered immunological responses in hypertensives, both clinical studies and basic animal research reported immunological aberrations in hypertension. For instance, serum immunoglobulin (Ig) levels are elevated in 20–40% of essential hypertensives, and these patients show altered humoral and cellular immunue functions (see for a review, Dzielak, 1992). Moreover, immunotherapy prevented hypertension in 50% of spontaneous hypertensive rats (SHR), and thymic implants form normotensive rat strains lowered blood pressure in SHR, delayed hypertension onset, and attenuated final hyperten-

sive state, suggesting a possible role of altered immunological system in the etiology of essential hypertension (Norman et al., 1985).

There is sufficient empirical ground to speculate that a central stress related mechanism underlies the enhanced activation of all three systems. This mechanism putatively involves corticotropin-releasing factor (CRF; released from the paraventricular nucleus of the hypothalamus), which interacts in multiple direct and indirect ways with the sympathetic catecholaminergic system (especially involving the norepinephrine-synthesizing locus ceruleus). This interaction, usually implying reciprocal stimulation under stress, is suggested to start a concerted response to a stressor, involving sympathoadrenal and HPA axis systems (al'Absi and Arnett, 2000; Lovallo et al., 1990), but also enhancing immune responses (Benschop et al., 1996). Indeed, recently it has been demonstrated that hypertensive patients have an elevated number of CRF containing neurons in the paraventricular nucleus (Goncharuk et al., 2002).

A few limitations of our experiment are noted, and may be further addressed in future studies. First, our study was mainly concerned with simultaneous activation of the three physiological systems and their covariation across tasks. However, the fixed order of the presentation of the tasks requires substantial prudence regarding interpretation of task specific effects. In addition, although diurnal effects on cortisol levels were largely accounted for by statistical control for baseline levels and the time of the experiment, the possibility cannot be excluded that systematic differences between the hypertensive and normotensive groups regarding diurnal rhythm over the 2-h experimental period existed and biased the cortisol data (Rosmond and Bjorntorp, 1998). An inclusion of a rest day for assessment of the exact diurnal rhythm for each individual would exclude this potential bias and is recommended for future studies. Saliva samples were taken at 5 min after the tasks, while it is known that cortisol peaks at approximately 20 min after a stressor. In addition to the relatively small sample size, this may have limited the effect sizes and thus attenuated differences between the groups. Finally, S-IgA data were controlled for salivary flow rate by correcting for changes in total protein concentrations. One drawback of this approach is that protein secretion and S-IgA secretion may share variance other than caused by changes in flow rate. This might also result in an attenuation of the observed effects.

Given the findings of the present study and suggestions regarding the role of the HPA and immune systems in essential hypertension (al'Absi and Arnett, 2000; Dzielak, 1992; Litchfield et al., 1998; Norman et al., 1985; Watt et al., 1992), the present findings warrant further research. Hence basic animal research, and experimental laboratory and longitudinal cohort studies with humans seem to hold promise for gaining more insight into the exact physiological mechanisms, pathophysiological consequences, and the direction of causality regarding the observed associations between generalized physiological hyperresponsivity and hypertension.

Acknowledgment

The authors would like to thank Dr. Clemens Kirschbaum from the University of Dresden, Germany, for taking care of the analyses of the cortisol samples.

References

al'Absi, M., Arnett, D.K., 2000. Adrenocortical responses to psychological stress and risk for hypertension. Biomedicine and Pharmacotherapy 54, 234–244.

al'Absi, M., Lovallo, W.R., McKey, B., Sung, B.H., Whitsett, T.L., Wilson, M.F., 1998. Hypothalamic–pituitary–adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. Psychosomatic Medicine 60, 521–527.

al'Absi, M., Lovallo, W.R., McKey, B.S., Pincomb, G.A., 1994. Borderline hypertensives produce exaggerated adrenocortical responses to mental stress. Psychosomatic Medicine 56, 245–250.

Amit, Z., Galina, Z.H., 1988. Stress-induced analgesia plays an adaptive role in the organization of behavioral responding. Brain Research Bulletin 21, 955–958.

Baumann, R., Ziprian, H., Gödicke, W., Hartrodt, W., Naumann, E., Läuter, J., 1973. The influence of acute psychic stress situations on biomedical and vegetative parameters of essential hypertensives at the early stage of the disease. Psychotherapy and Psychosomatics 22, 131–140.

Benschop, R.J., Rodriguez-Feuerhahn, M., Schedlowski, M., 1996. Catecholamine-induced leukocytosis: early observations, current research, and future directions. Brain, Behavior, and Immunity 10, 77–91.

Bohlin, G., Eliasson, K., Hjemdahl, P., Klein, K., Fredrikson, M., Frankenhaeuser, M., 1986. Personal control over work pace: circulatory, neuroendocrine and subjective responses in borderline hypertensives. Journal of Hypertension 4, 295–305.

Bosch, J.A., Berntson, G.G., Cacioppo, J.T., Dhabhar, F.S., Marucha, P.T., 2003a. Acute stress evokes selective redistribution of T lymphocytes that differ in chemokine receptor expression: a possible pathway linking reactivity with cardiovascular disease. Brain, Behavior, and Immunity 17, 251–259.

Bosch, J.A., Brand, H.S., Ligtenberg, T.J.M., Bermond, B., Hoogstraten, J., Nieuw Amerongen, A.V., 1996. Psychological stress as a determinant of protein levels and salivary-induced aggregation of *streptococcus gordonii* in human whole saliva. Psychosomatic Medicine 58, 374–382.

Bosch, J.A., de Geus, E.J.C., Kelder, A., Veerman, E.C.I., Hoogstraten, J., Nieuw Amerongen, A.V., 2001. Differential effects of active versus passive coping on secretory immunity. Psychophysiology 38, 836–846.

Bosch, J.A., de Geus, E.J.C., Veerman, E.C.I., Hoogstraten, J., Nieuw Amerongen, A.V., 2003b. Innate secretory immunity in response to laboratory stressors that evoke distinct patterns of cardiac autonomic activity. Psychosomatic Medicine 65, 245–258.

Bosch, J.A., Ring, C., de Geus, E.J.C., Veerman, E.C.I., Nieuw Amerongen, A.V., 2002. Stress and secretory immunity. International Review of Neurobiology 52, 213–254.

Brod, J., 1963. Hemodynamic basis of acute pressor reactions and hypertension. British Heart Journal 25, 227–245.

Cacioppo, J.T., Berntson, G.G., Malarkey, W.B., Kiecolt-Glaser, J.K., Sheridan, J.F., Poehlmann, K.M., Burleson, M.H., Ernst, J.M., Hawkley, L.C., Glaser, R., 1998. Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. In: McCann, S.M., Sternberg, E.M., Lipton, J.M., Chrousos, G.P., Gold, P.W., Smith, C.C. (Eds.), Neuromodulation: Molecular Aspects, Inte-

grative Systems, and Clinical Advances. Annals of the New York Academy of Sciences, vol. 840. New York Academy of Sciences, New York, pp. 664–673.

Chen, C.-M., Schachter, D., 1993. Elevation of plasma immunoglobulin A in the spontaneously hypertensive rat. Hypertension 21, 731–738.

Dressendörfer, R.A., Kirschbaum, C., Rohde, W., Stahl, F., Strasburger, C.J., 1992. Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. Journal of Steroid Biochemical and Molecular Biology 43, 683–692.

Dzielak, D.J., 1992. The immune system and hypertension. Hypertension 19 (Suppl.), I-36–I-44.

Eich, R.H., Cuddy, R.P., Smulyan, H., Lyons, R.H., 1966. Hemodynamics in labile hypertension: a follow-up study. Circulation 34, 299–307.

Elenkov, I.J., Wilder, R.L., Chrousos, G.P., Vizi, E.S., 2000. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. Pharmacology Reviews 52, 595–638.

Eliasson, K., Hjemdahl, P., Kahan, T., 1983. Circulatory and sympathoadrenal responses to stress in borderline and established hypertension. Journal of Hypertension 1, 131–139.

Esler, M., Julius, S., Zweifler, A., Randall, O., Harburg, E., Gardiner, H., DeQuattro, V., 1977. Mild high-renin essential hypertension neurogenic human hypertension? New England Journal of Medicine 296, 405–411.

Fahrenberg, J., Foerster, F., Wilmers, F., 1995. Is elevated blood pressure level associated with higher cardiovascular responsiveness in laboratory tasks and with response specificity? Psychophysiology 32, 81–91.

Fredrikson, M., Matthews, K.A., 1990. Cardiovascular responses to behavioral stress: a meta-analytic review. Annals of Behavioral Medicine 12, 30–39.

Fredrikson, M., Tuomisto, M., Bergman-Losman, B., 1991. Neuroendocrine and cardiovascular stress reactivity in middle-aged normotensive adults with parental history of cardiovascular disease. Psychophysiology 28, 656–664.

Goncharuk, V.D., Van Heerikhuize, J., Swaab, D.F., Buijs, R.M., 2002. Paraventricular nucleus of the human hypothalamus in primary hypertension: activation of corticotropin-releasing hormone neurons. Journal of Comparative Neurology 443, 321–331.

Guzzetti, S., Piccaluga, E., Casati, R., Cerutti, S., Lombardi, F., Pagani, M., Malliani, A., 1988. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. Journal of Hypertension 6, 711–717.

Hettema, J., Van Heck, G.L., Brandt, C., 1989. The representation of situations through films. In: Hettema, J. (Ed.), Personality and Environment: Assessment of Human Adaptation. Wiley, New York, pp. 114–127.

Hollenberg, N.K., Williams, G.H., Adams, D.F., 1981. Essential hypertension: abnormal renal vascular and endocrine responses to a mild psychological stimulus. Hypertension 3, 11–17.

Julius, S., 1991. Autonomic nervous system dysregylation in human hypertension. American Journal of Cardiology 67, 3b–7b.

Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology 22, 150–169.

Krantz, D.S., Helmers, K.F., Bairey, C.N., Nebel, L.E., Hedges, S.M., Rozanski, A., 1991. Cardiovascular reactivity and mental stress-induced myocardial ischemia in patients with coronary artery disease. Psychosomatic Medicine 53, 1–12.

Light, K.C., Dolan, C.A., Davis, M.R., Sherwood, A., 1992. Cardiovascular responses to an active coping challenge as predictors of blood pressure patterns 10 to 15 years later. Psychosomatic Medicine 54, 217–230.

Litchfield, W.R., Hunt, S.C., Jeunemaitre, X., Fisher, N.D.L., Hopkins, P.N., Williams, R.R., Corvol, P., Williams, G.H., 1998. Increased urinary free cortisol: a potential intermediate phenotype of essential hypertension. Hypertension 31, 569–574.

Lovallo, W.R., Pincomb, G.A., Brackett, D.J., Wilson, M.F., 1990. Heart rate reactivity as a predictor of neuroendocrine responses to aversive and appetitive challenges. Psychosomatic Medicine 52, 17–26.

Manuck, S.B., Kasprowicz, A.L., Muldoon, M.F., 1990. Behaviorally-evoked cardiovascular reactivity and hypertension: conceptual issues and potential associations. Annals of Behavioral Medicine 12, 17–29.

Mills, P.J., Farag, N.H., Hong, S., Kennedy, B.P., Berry, C.C., Ziegler, M.G., 2003. Immune cell CD62L and CD11a expression in response to a psychological stressor in human hypertension. Brain, Behavior, and Immunity 17, 260–267.

Neville, A.M., O'Hare, M.J., 1984. The Human Adrenal Cortex. Springer Verlag, New York.

Norman Jr., R.A., Dzielak, D.J., Bost, K.L., Khraibi, A.A., Galloway, P.G., 1985. Immune system dysfunction contributes to the aetiology of spontaneous hypertension. Journal of Hypertension 3, 261–268.

Nyklíček, I., Vingerhoets, A.J.J.M., Van Heck, G.L., 1999a. Elevated blood pressure and self-reported symptom complaints, daily hassles, and defensiveness. International Journal of Behavioral Medicine 6, 177–189.

Nyklíček, I., Vingerhoets, A.J.J.M., Van Heck, G.L., 1999b. Hypertension and pain sensitivity: effects of gender and cardiovascular reactivity. Biological Psychology 50, 127–142.

Proctor, G.B., Carpenter, G.H., 2002. Neural control of salivary S-IgA secretion. International Reviews of Neurobiology 52, 187–212.

Rosmond, R., Bjorntorp, P., 1998. Blood pressure in relation to obesity, insulin, and the hypothalamus–pituitary–adrenal axis in Swedish men. Journal of Hypertension 16, 1721–1726.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrinology Reviews 21, 55–89.

Shapiro, D., Jamner, L.D., Lane, J.D., Light, K.C., Myrtek, M., Sawada, Y., Steptoe, A., 1996. Blood pressure publication guidelines. Psychophysiology 33, 1–12.

Tuomisto, M., 1997. Intra-arterial blood pressure and heart rate reactivity to behavioral stress in normotensive, borderline, and mild hypertensive men. Health Psychology 16, 554–565.

Tursky, B., 1974. Physical, physiological, and psychological factors that affect pain reaction to electric shock. Psychophysiology 11, 95–112.

Uchino, B.N., Cacioppo, J.T., Malarkey, W., Glaser, R., 1995. Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. Journal of Personality and Social Psychology 69, 736–743.

Van Zijderveld, G.A., Van Doornen, L.J.P., Van Faassen, I., Orlebeke, J.F., Van Dyck, R., Tilders, F.J.H., 1993. Adrenaline and the relationship between neurosomatism, aerobic fitness and mental task performance. Biological Psychology 36, 157–181.

Walker, B.R., Best, R., Shackleton, C.H.L., Padfield, P.L., Edwards, C.R.W., 1996. Increased vasoconstrictor sensitivity to glucocorticoids in essential hypertension. Hypertension 27, 190–196.

Watt, G.C., Harrap, S.B., Foy, C.J., Holton, D.W., Edwards, E.V., Davidson, H.R., Connor, J.M., Lever, A.F., Fraser, R., 1992. Abnormalities of glucocorticoid metabolism and the rennin-angiotensin system: a four corners approach to the identification of genetic determinants of blood pressure. Journal of Hypertension 10, 473–482.